LEADING ARTICLE

Catheter-Related Infections in Intensive Care Units: An Overview with Special Emphasis on Prevention

Philippe Eggimann and Didier Pittet
Department of Internal Medicine, University of Geneva Hospitals, Geneva, Switzerland

Catheter-related infection remains a leading cause of nosocomial infections, particularly in intensive care units. It includes colonization of the device, skin exit-site infection, and device- or catheter-related bloodstream infection. The last-mentioned represents the most frequent life-threatening associated complication of central venous catheter (CVC) use and is associated with significant patient morbidity, mortality, and extra hospital costs. The incidence of catheter-related bloodstream infection ranges from 2–14 episodes per 1000 catheter-days. On average, microbiologically documented device-related bloodstream infections complicate 3–5 per 100 CVC uses; however, they represent merely the tip of the iceberg, and most cases of clinical sepsis are nowadays considered to be catheter-related. This article will briefly review the pathophysiology of these infections, highlighting the importance of the skin insertion site and the intravenous line hub as principal sources of colonization. A short review of the principles of therapy is also provided. The latest preventive approaches are presented in more detail, including the possible benefit of recently developed impregnated catheters and the positive impact of educational programs and/or a global preventive strategy based on strict application of preventive measures and on careful control of all factors associated with catheter-related infection. This may help clinicians to determine the eventual necessity to incorporate them in their own practice.

According to the Institute of Medicine in Washington, DC, USA, preventable adverse events in the United States, including nosocomial infections, are responsible for 44 000–98 000 deaths annually and represent a cost of US$17–29 billion [1]. Among them, nosocomial infections now concern 5–15% of hospitalized patients and can lead to complications in 25–50% of those admitted to intensive care units (ICUs) [2]. Pneumonia related to mechanical ventilation, intra-abdominal infections following trauma or surgery, and bacteremias or sepsis related to intravascular devices account for more than 80% of these [3,4].

In the United States, it is estimated that up to 150 million intravascular devices are inserted into hospitalized patients, and that 200 000–400 000 nosocomial bloodstream infections (BSIs) may occur each year [3]. The National Nosocomial Infection Surveillance (NNIS) system reported that most of these infections are related to intravascular access, with rates substantially higher among patients with central venous catheters (CVCs) than among those with peripheral lines [3,4]. Overall, a central line is reported to be present in 50% of ICU patients, and micro-organisms eventually colonize 25% of these lines [5–7]. Rates of infections range between 2.8 and 12.8 episodes per 1000 catheter-days and may have a significant impact on patient morbidity and hospital costs in ICUs [4,8].

However, a large proportion of catheter-related infections (CRIs) are preventable [9]. The newly developed catheters coated with antiseptic(s) or antibiotic(s) may represent a major advance in prevention [7,10]. Moreover, recent data strongly suggest that a global preventive strategy and/or educational programs including a careful control of all factors associated with CRIs may also be very effective [11,12].

Address for correspondence: Professor Didier Pittet, Infection Control Program, Department of Internal Medicine, University of Geneva Hospitals, 1211 Geneva 14, Switzerland.

Epidemiology and impact

CRIs include colonization of the device, skin exit-site infection, and device-related BSI (Table 1). Accordingly, the epidemiology varies considerably depending on the type of device, its localization, and the purpose for which it is used [13].

The most available data concern BSIs. These represented 12% of all nosocomial infections reported in 10 038 patients from 1417 ICUs in the European Prevalence of Infection in Intensive Care (EPIC) study [13]. In a review of 30 prospective studies, Hampton and Sherertz [14] reported the risk of CRI per day of catheterization to be 1.3%, 1.9%, and 3.3%, respectively, for venous peripheral, arterial, and venous central lines. Data extracted from recent studies indicate that the microbiologically documented catheter-related bloodstream infection (CR-BSI) rate with all CVCs averages 5% [5–7,15]. (Table 2). In addition, incidence-density CVC-BSI rates allow comparisons between different types of ICUs (Table 3).

Case-control studies have attempted to estimate the impact of CRIs (Table 4). In a study of nosocomial BSI in critically ill patients [8], significantly different mortality rates were observed between patients with BSIs acquired in a surgical ICU (50%) and closely-matched controls (15%), corresponding to an attributable mortality of 35% (95% CI 25–45). In the subgroup of patients with CR-BSIs, the attributable mortality was 25%, with additional ICU stay and extra costs of 6.5 days and US$28 690, respectively [16]. In two recent studies, DiGiovine et al. [17] and Rello et al. [18] reported no attributable mortality (crude mortality 35% vs. 31%, and 22% vs. 35%, respectively) but significant increases in both length of stay (10 and 20 days, respectively) and in costs (US$16 000 and US$4000 per episode, respectively). Overmatching may, however, have played a role in these studies, with possible undervaluation of estimates. Thus, assessing the precise impact of CRI and CR-BSI is now crucial. However, it will be necessary to control not only for the severity of disease, but also for the type and duration of catheter use and care, as well as for other major confounding factors of outcome.

Diagnosis and microbiology

As local signs may be completely absent, clinical diagnosis of CVC-related infection may be difficult. In addition, thrombophlebitis may be of non-infectious origin, making these signs neither sensitive nor specific.

Table 1. Definitions of catheter-related infections.

Type of condition	Definitions
Catheter colonization	In the absence of clinical signs of infection at the skin insertion site: • Quantitative culture — <100 colony-forming units (CFUs) (Brun-Buisson) • Quantitative culture — $<10^3$ CFUs (vortex) • Semi-quantitative culture — <15 CFUs (roll-plate technique)
Exit-site infection	At the insertion skin site of any vascular access: • Microbiologically documented — a positive (semi-) quantitative catheter culture in the presence of clinical signs of infection (erythema, tenderness, induration, or purulence) • Clinically documented — a clinical infection (erythema, tenderness, induration, or purulence)
Bloodstream infection	• Primary bloodstream infection — refers to a bacteremia (or fungemia) for which there is no documented distal source, and includes those resulting from an intravenous or arterial line infection • Clinical sepsis — one of the following clinical signs or symptoms with no other recognized cause: - fever (>38°C) - hypotension (systolic blood pressure ≤90 mmHg) - oliguria (>20 ml/h) and all of the following: - blood culture not performed or no organism detected in blood - no apparent infection at another site - clinical response to appropriate empirical antimicrobial therapy after vascular access removal and/or change
Catheter-related bloodstream infection	• Isolation of the same organism (i.e. identical species, antibiogram) from a quantitative culture of the distal catheter segment and from the blood of a patient with clinical symptoms of sepsis and no other apparent source of infection • In the absence of catheter culture, defervescence after removal of an implicated catheter from a patient with primary bloodstream infection is considered as indirect evidence of catheter-related bloodstream infection

Adapted from [61].

Various methods for culturing the insertion site, the catheter, and the blood have been described, and a choice must be made according to preferred sensitivity and specificity, both varying between 78% and 95% [19] (Table 5).

Most micro-organisms implicated in CRIs arise from the skin flora (Table 6). Gram-positive cocci are responsible for at least two-thirds of infections. Coagulase-negative staphylococci are the leading bacteria cultured from catheters, but enterococci are not uncommon [7,15,20].

Table 2. Colonization and catheter-related bloodstream infection rates in selected ICU series with impregnated and non-impregnated central venous lines.

Type of catheter Author [ref]	Number in study	Catheter colonization number (%)		Catheter-related bloodstream infections number (%)	
Non-impregnated					
Bach et al. [62] *	117	36	(30.8)	3	(2.6)
Hannan et al. [63] **	177	71	(40.1)	8	(4.5)
Heard et al. [15] ***	157	82	(52.2)	6	(3.8)
Loo et al. [64] †	81	25	(30.9)	3	(3.7)
Maki et al. [5] ††	195	47	(24.1)	9	(4.6)
Marik et al. [65] †††	39	11	(28.2)	2	(5.1)
Raad et al. [6] ‡	136	32	(23.5)	7	(5.1)
Tennenberg et al. [20] ‡‡	145	32	(22.1)	9	(6.6)
van Heerden [66] ‡‡‡	26	10	(38.5)	0	-
Silver-sulfadiazine/chlorhexidine impregnated					
Bach et al. [62] *	116	21	(18.1)	0	-
Hannan et al. [63] **	174	47	(27.0)	3	(1.7)
Heard et al. [15] ***	151	60	(39.7)	5	(3.3)
Loo et al. [64] †	77	12	(15.6)	3	(3.9)
Maki et al. [5] ††	208	28	(13.5)	2	(1.0)
Marik et al. [65] †††	36	7	(19.4)	1	(2.8)
Tennenberg et al. [20] ‡‡	137	8	(5.8)	5	(3.7)
van Heerden [66] ‡‡‡	28	4	(14.3)	0	-
Darouiche [7] §	382	87	(22.8)	13	(3.4)
Minocyclin/rifampin impregnated					
Marik et al. [65] **	38	4	(10.5)	0	-
Raad et al. [6] ‡	130	11	(8.5)	0	-
Darouiche et al. [7] §	356	28	(7.9)	1	(0.3)

* Quantitative level of bacterial colonization 52±17 vs. 256±86 colony-forming units (CFUs) for silver-sulfadiazine/chlorhexidine-impregnated as compared with non-impregnated catheters, respectively; p<0.05. No significant differences for catheter-related bloodstream infections.

** Semi-quantitative analysis of bacterial counts for colonization of silver-sulfadiazine/chlorhexidine-impregnated as compared with non-impregnated catheters; p<0.01. No significant differences for catheter-related bloodstream infections.

*** Odds ratio for colonization only: 0.59 (95% CI 0.34–0.97) for silver-sulfadiazine/chlorhexidine-impregnated as compared with non-impregnated catheters, respectively; p=0.04.

† Catheter-tip positive cultures for silver-sulfadiazine/chlorhexidine-impregnated as compared with non-impregnated catheters; p<0.05. No significant differences for catheter-related bloodstream infections.

†† Odds ratio for colonization: 0.56 (95% CI 0.36–0.89) for silver-sulfadiazine/chlorhexidine-impregnated as compared with non-impregnated catheters, respectively; p<0.005. Odds ratio for catheter-related bloodstream infection: 0.21 (95% CI 0.03–0.95) for silver-sulfadiazine/chlorhexidine-impregnated as compared with non-impregnated catheters, respectively; p=0.03.

††† Semi-quantitative cultures of distal segment for minocyclin/rifampin-coated as compared with non-impregnated catheters; p=0.5. No significant differences for catheter-related bloodstream infections.

‡ Odds ratio for colonization: 0.25 (95% CI 0.12–0.53) for minocyclin/rifampin-coated as compared with non-impregnated catheters, respectively; p<0.001. The rates of catheter-related bloodstream infection per 1000 catheter-days were 7.34 for non-impregnated and 0 for impregnated catheters (p<0.01; binomial exact test).

‡‡ Risk reduction for colonization only: 43% for silver-sulfadiazine/chlorhexidine-impregnated as compared with non-impregnated catheters, respectively; p<0.001.

‡‡‡ Semi-quantitative cultures of distal segment for silver-sulfadiazine/chlorhexidine-impregnated as compared with non-impregnated catheters, respectively, p<0.05. No significant differences for catheter-related bloodstream infections.

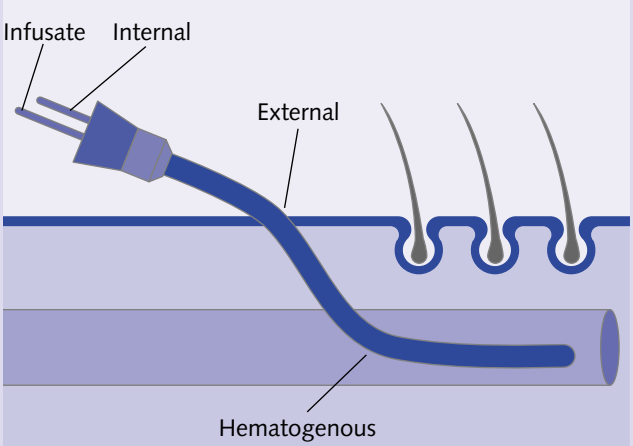
§ Odds ratio for colonization: 0.35 (95% CI 0.23–0.52) for minocyclin/rifampin-impregnated as compared with silver-sulfadiazine/chlorhexidine-impregnated catheters, respectively; p<0.001. Odds ratio for catheter-related bloodstream infection: 0.08 (95% CI 0.01–0.63) for minocyclin/rifampin-impregnated as compared with silver-sulfadiazine/chlorhexidine-impregnated catheters, respectively; p<0.0001.

Staphylococcus aureus (*S. aureus*) is responsible for 5–15% of the infections and is associated with a higher rate of complications [21]. Gram-negative bacilli may colonize invasive monitoring pressure systems, orotracheal cavities, and complicated remote infections, particularly in critically ill patients [22]. *Candida* species have emerged as an important source of CRIs, and account for a high proportion of the dramatic increase in the rate of candidemia over the last decade [3].

Pathogenesis and risk factors

Four distinct pathways may be identified in the development of CRI (Fig. 1) [3]. External surface pathway infection may start with the colonization of the insertion site by micro-organisms that may move by capillary action through the transcutaneous part of the dermal tunnel surrounding the catheter. Internal surface pathway infection may occur by colonization of the hub and intraluminal surface of the catheter [23]. Host glycoproteins, such as fibrinogen, fibronectin, collagen, and laminin, adsorbed on the surface of intravenous devices, form a layer that enhances bacterial adherence — in particular, *S. aureus* and coagulase-negative staphylococci — to foreign material. In addition, some strains produce a mucoid exopolymeric substance (slime), conferring them some protection against antimicrobials and interfering with neutrophil function [24]. Skin colonization is a strong predictor of CRIs [22,25]. Frequent opening of the hub is now viewed as an important source of colonization [5,7,26]. Additional risk factors predisposing to colonization and infection are catheter material, line insertion, localization, and type of care. Hematogeneous seeding of the catheter during BSI of any origin represents a third pathway of CRIs [9]. Finally, contamination of the fluids or drugs intravenously administered constitutes another pathway of CRIs, sometimes responsible for outbreaks [3].

Figure 1. Colonization pathways involved in intravenous-catheter-related infection. External and internal catheter surface colonization pathways involve colonization of the skin insertion site and hub, respectively. Additional pathways include microbial contamination of the infusate (so-called intrinsic contamination), and hematogeneous seeding.



Treatment

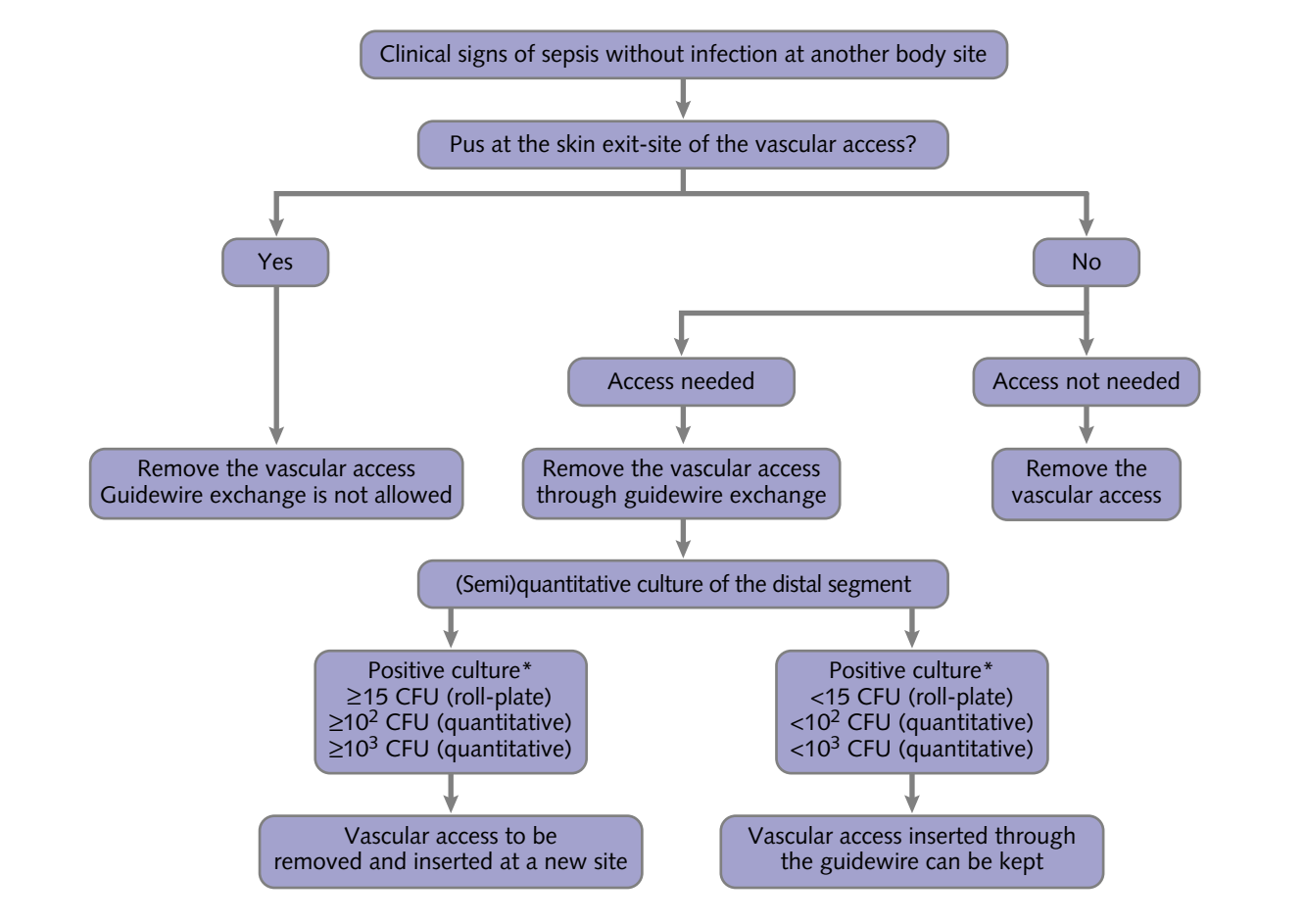
Removal of a catheter suspected to be infected is strongly recommended. Catheter retention may result in a several-fold higher risk for recurrence of BSI. Removal is mandatory in severe or complicated infections such as shock, persistent fever or bacteremia, or with certain micro-organisms (*S. aureus*, Gram-negative bacilli, *Candida* spp) [3,27].

However, systematic removal of a CVC with insertion at a new site was proven to be unnecessary in 75% to 90% of cases [9,28,29]. This may, in part, explain why catheter exchange over a guidewire has been generalized in most ICUs. This technique may increase the likelihood of infection of the new catheter, but reduces the rate of complications associated with CVC placement in a new site, which may be technically difficult in some severely ill patients requiring multiple vascular accesses [28]. Randomized prospective studies have failed to detect any preventive benefit associated with guidewire exchange compared with insertion at a new site [29]. However, it is the opinion of many experts that this technique can be performed in critically ill patients with limited sites for new vascular access, but meticulous aseptic technique is imperative [9]. Practically, our opinion is that guidewire exchange together with systematic (semi-) quantitative culture of the catheter tip is mandatory in any case of sepsis without clinical evidence of another source of infection [12]. Removal of the exchanged catheter followed by further insertion at a new site is then absolutely indicated in the presence of a positive culture of the removed material (Fig. 2). The possible benefit of concomitant antibiotic administration at time of catheter replacement needs to be investigated.

Several studies have reported successful conservative treatment of CRIs, particularly bacteremia due to coagulase-negative staphylococci, without removal of the catheter. The technique of antibiotic-lock may be particularly helpful in avoiding difficult vascular access replacement in patients with implanted or permanent devices [30].

Although some authors recommend no treatment once the catheter is removed, many authorities prefer to

Figure 2. Approach to a patient with clinical sepsis suspected to be related to a vascular access site.



*Cut-off values vary with the technique used for the diagnosis [22,83,84] (Table 5).
CFU: colony-forming units

treat with an appropriate antibiotic course (5–7 days for uncomplicated coagulase-negative staphylococci). In patients with CRIs caused by *S. aureus*, treatment duration should be 10–14 days, although recent data have suggested that a transesophageal echocardiogram may help to identify vegetation(s) that requires a specific management in a significant proportion of patients [31].

Relapse, continuous fever, or bacteremia despite removal of the catheter involves an active search for complications such as another line-associated infection, metastatic abscess, septic thrombophlebitis, or endocarditis. Following treatment completion, careful follow-up is required owing to the frequent occurrence of late complications [3,25].

Prevention

More than 50% of patients admitted to ICUs are, at the time of admission, already colonized with the organism responsible for subsequent infection, although some of them will acquire it from the environment [32]. Nevertheless, the prevention of CRIs relies on a careful control of all the factors associated with the colonization of vascular accesses by micro-organisms. Evidence-based guidelines and preventive measures were published by the Hospital Infections Control Practices Advisory Committee in 1996 [9]. This topic was also recently extensively reviewed elsewhere [33,34].

Despite these recommendations, the rates of CRIs did not significantly decrease until the development of antibiotic/antiseptic-coated catheters (Table 2), and, more recently, by the application of educational programs (Table 7).

Antibiotic- and antiseptic-coated catheters

Intraluminal antibiotic locks or flushes with vancomycin have been reported to reduce the rate of CRIs, but only few studies have been conducted in ICU patients [35]. Moreover, the use of antibiotics for this purpose could lead to the emergence of vancomycin-resistant Gram-

positives, which must be avoided because glycopeptide antibiotics are the only drugs available for the treatment of infections due to methicillin-resistant staphylococci and penicillin-resistant enterococci [9].

Two prospective, randomized clinical studies [5,6] suggested that the use of CVCs impregnated with either chlorhexidine and silver sulfadiazine or minocycline and rifampin was associated with a significant reduction of microbiologically documented CRIs — 44% and 79%, respectively. These results were confirmed by another study [15] and a recently published meta-analysis [10]. In addition, a cost-effectiveness analysis based on the results of this meta-analysis suggested that the use of chlorhexidine/sulfadiazine-impregnated catheters decreased the absolute incidence of CR-BSI ranged from 1.2% to 3.4%, corresponding to a cost saving of US$68 to US$391 per catheter used [36].

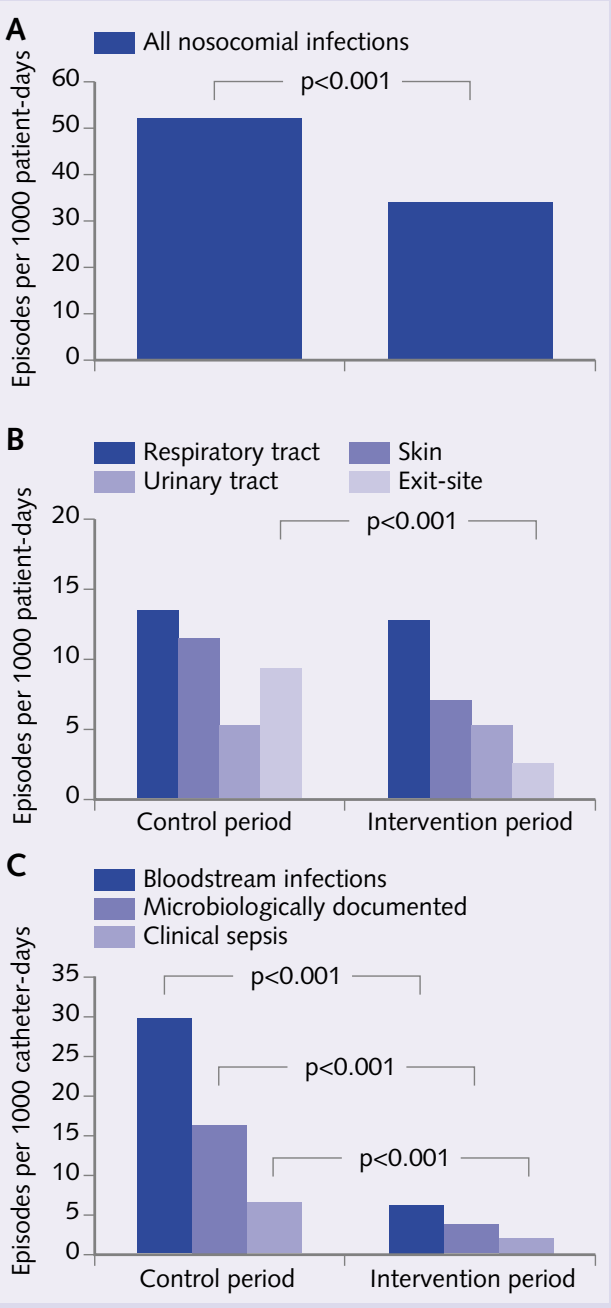
A direct comparison between these new materials was subsequently undertaken in a multicenter study [7]. The minocycline/rifampin-impregnated catheter was reported to be associated with significantly lower colonization (relative risk [RR] 0.35; 95% CI 0.24–0.55) and CR-BSIs (RR 0.08; 95% CI 0.01–0.63). The authors argued that this difference may be due, in part, to the absence of chlorhexidine and silver sulfadiazine in the intraluminal surface. This is consistent with another study in which the silver/chlorhexidine catheters were not associated with a reduction of the CRI rate [37]. Furthermore, data from a study that evaluated colonization and residual *ex vivo* antimicrobial activity after removal of 113 CVCs that were no longer required, strongly favors this hypothesis [38]. However, the time of catheterization may have played a role. Impregnated catheters failed to prevent CRIs in neutropenic cancer patients with a mean catheterization time of 20 days as compared with 6, 7, and 8.3 days for the previously mentioned studies [5–7,37]. A meta-analysis confirmed that the potential benefit of these devices may be lost after 7 to 10 days [39].

Educational programs

Sherertz et al. [11] recently reported that an educational program for physicians-in-training can also decrease the risk for CRIs. A 1-day course on infection control practices and on procedures of vascular access insertion was shown to reduce the infection rate by 27%, from 3.3 to 2.4 per 1000 CVC-days (Table 3).

A recent study evaluated the impact of a global strategy targeted at the reduction of CRIs in 3154 critically ill patients consecutively admitted to a medical ICU [12]. Following the introduction of this educational program, the incidence-density of exit-site catheter infection

Figure 3. Incidence of nosocomial infections before and after the implementation of a global strategy targeted at vascular access care. A: effect on all nosocomial infections (p<0.0001). B: effect on respiratory tract infections (p=0.75); on skin or mucous membranes (p=0.02); on urinary tract infections (p=1.0); on skin exit-site infections (p<0.0001). C: effect on bloodstream infections expressed as episodes per 1000 catheter-days (p<0.0001) due to the effect both on primary bloodstream infections (p<0.001) and on clinical sepsis (p<0.001).



Adapted from [12].

Table 3. CVC-related nosocomial infection rates in selected ICUs.

Author [ref]	Type of ICU	Period	Number of units	Bloodstream infections per 1000 CVC-days	
NNIS [4]	Medical	1997–1999	135	5.3	(3.6–7.1) *
	Coronary	1997–1999	112	4.0	(1.7–6.3) *
	Surgical	1997–1999	157	5.1	(2.6–7.0) *
	Pediatric	1997–1999	73	6.9	(4.1–9.3) *
Eggimann et al. [12]	Medical	1997	1	2.3 **	-
	Medical	1996	1	6.6	-
Sherertz et al. [11]	Mixed	1997	6	2.4 ***	-
	Mixed	1996	6	3.3	-
Legras et al. [67]	Mixed	1995	5	4.8	-
Singh-Naz et al. [68]	Pediatric	1993	1	8.9	-
	Pediatric	1995	1	16.8	-
Gastmeier et al. [69]	Neonatology	1997	1	12.5	-
Finkelstein et al. [70]	Mixed	1998	1	12.0	-
Simon et al. [71]	Pediatric	1998	1	10.7	-
Weber et al. [72]	Burn	1990–1991	1	4.9	-
Dettenkoffer et al. [73]	Neurosurgical	1997–1998	1	0.9	-

* 50th percentile (25th–75th).
** After the implementation of a global strategy targeted at the reduction of catheter-related infections.
*** After the implementation of an educational program targeted at the reduction of catheter-related infections.

Table 4. Impact of nosocomial bloodstream infections (BSIs) in selected groups of patients.

Author [ref]	Year of publication	Study period	Number of cases	Mortality Type of BSI	Crude (%)	Attributable (%)	Attributable LOS *(days)	Costs (US$)
Hospital-wide								
Rose et al. [74]	1977		40	Nosocomial **	38.0	28	11.0	4400
Spengler [75]	1978	1972–1974	99	Nosocomial **	32.9	28	9.0	5800
Wey et al. [76]	1988	1983–1986	88	Candidemia	57.0	38		
Martin et al. [77]	1989	1984–1987	118	Nosocomial ***	30.5	17	8.5	
ICUs								
Forgacs et al. [78]	1986	1970–1985	468	Nosocomial **	60.4	47†		
Smith et al. [79]	1991	1986–1989	34	Nosocomial **	82.4	30		
Rello et al. [80]	1994	1990–1992	111	Nosocomial **	31.5	65†		
Pittet et al. [8]	1994	1988–1990	86	Nosocomial **	50.0	35	24.0	40 000
Pittet et al. [16]	1994	1988–1990	20	Catheter-related	45.0	25	6.5	29 000
Wisplinghoff et al. [66]	1999	1990–1992	29	Nosocomial ††	31.0	16	20.0	
Soufir et al. [81]	1999	1990–1995	38	Catheter-related	50.0	29		
DiGiovine et al. [17]	1999	1994–1996	68	Nosocomial †††	35.3	4§	10.0	35 000
Rello et al. [18]	2000	1992–1999	49	Catheter-related	22.4	13§	20.0	4000

* LOS: length of stay.
** Includes both primary and secondary bloodstream infections.
*** Primary coagulase-negative staphylococci (CNS) bacteremia only.
† Attributable mortality was not determined in a matched-control study, but by simple comparison with the crude mortality of all patients who did not develop a bloodstream infection.
†† *Acinetobacter baumannii* nosocomial bloodstream infections only.
††† Includes primary bloodstream infections only.
§ Differences are non-significant.

decreased by 64%, and that of BSI by 67%. Although the overall exposure to the CVC did not significantly differ between the control and the intervention periods (median duration, 4.1 vs. 3.9 days; p=0.94), the incidence-density of BSI markedly decreased from 22.9 to 6.2 episodes per 1000 CVC-days, owing to a reduced incidence of both microbiologically documented infection (from 6.6 to 2.3 episodes per 1000 CVC-days) and clinical sepsis

Table 5. Sensitivity and specificity of cultures performed for the diagnosis of catheter-related infection.

Type of culture *Methodology*	Sensitivity (%)	Specificity (%)
Rapid diagnosis		
Gram's stain and acridine-orange leukocyte cytospin test *	96	92
Direct microscopic examination of blood drawn through the suspected vascular access, and processed to be stained with acridine orange and Gram's stain [82]		
Catheter culture		
Qualitative catheter segment culture:	95	75
Colony-forming units (CFUs) are not counted		
Semi-quantitative catheter segment culture:	85	85
A 2-inch distal portion of the catheter is rolled four times over the surface of a sheep-blood agar plate and incubated for 48 h. Cut-off value >15 CFUs per segment (roll-plate technique) [22]		
Quantitative catheter segment culture:	94	92
Vortexing, sonicating, flushing, and vortexing the catheter with serial dilutions of the specimens obtained. Cut-off value >10^2–10^3 CFUs per segment [83,84]		
Blood cultures		
Standard blood cultures:	91	86
Two sets of blood cultures (two bottles each) with at least one drawn percutaneously		
Quantitative blood cultures:	79	94
Differential quantitative culture of two sets of blood cultures, one drawn percutaneously and the other through the suspected vascular access		
Differential-time blood cultures:	91	94
Differential time to positivity of two sets of blood cultures drawn simultaneously, percutaneously and from the suspected vascular access [85]		

Adapted from [19] and [82–85].

* Sensitivity and specificity were reported to be 87% and 94%, respectively, in a previous experience with acridine-orange leukocyte cytospin [86].

Table 6. Micro-organisms associated with device-related bloodstream infections.

	Proportion (%)
Common micro-organisms	
Coagulase-negative staphylococci	60–70
S. aureus	5–15
Candida spp	5–10
Enterobacteriaceae	5–10
Less common micro-organisms	
Enterococci	2–4
Methicillin-resistant *S. aureus*	2–4
Commonly responsible for outbreaks	
Burkholderia spp	<1
Malassezia spp	<1

(from 16.3 to 3.9 episodes per 1000 CVC-days) (Fig. 3). Overall, the incidence-density of nosocomial infections was reduced by 35% (from 52.4 to 34.0 episodes per 1000 patient-days), corresponding to the prevention of more than 75 nosocomial infections over an 8-month period, including at least 30 primary BSIs and 25 vascular access-related infections. It was estimated that this would also correspond to the annual salary of three full-time infection control nurses.

The impact in terms of reduction of nosocomial infections in these two studies was largely superior to that expected with the use of antimicrobial/antisepsis-coated catheters [10,36]. Thus, behavioral changes may have played a key role in the success of these educational programs, which were based on a multimodal and multidisciplinary approach including communication and education tools, active participation and positive feedback, and systematic involvement of the leaders [40,41].

Specific guidelines

Specific guidelines included in the global strategy implemented through an educational program targeted at vascular access care are presented in Table 7. Most of them are supported by clinical studies with limited strength of evidence. In the absence of randomized double-blind trials, some of them are discussed in the following paragraphs.

The program consisted of slide-show-based educational sessions and bedside training of all the staff including nurses (Figs. 4–6).

Hand-hygiene measures

As is the case for other nosocomial infections, prevention is mostly based on a strict application of the concepts of standard precautions [42]. A strict adherence to hand-hygiene measures (hand washing and/or hand

Table 7. Guidelines for insertion and handling of vascular accesses in intensive care unit patients to prevent the development of catheter-related infections

Hygiene	Hand disinfection	Strongly emphasized for any care (http://www.hopisafe.ch)
	Hand washing	Restricted for dirty hand, followed by hand disinfection
Material	Preparation	Material disposed according to detailed listing to avoid interruptions during the insertion *
Patient	Installation	Patient and devices are disposed in order to manage sufficient access to the insertion site for the operator
Insertion	Skin preparation	Hair cutting instead of shaving
	Antisepsis	Alcohol-based (60–70%) solution of chlorhexidine gluconate 0.5%
	Technique	Maximal barrier precautions: sterile gown and gloves, cap, surgical mask, large sterile drapes
	Site	Promotion of subclavian (CVC) and wrist vein (short lines) sites
	Fixation	Promotion of simple node at the exit site, without special fixing device (Fig. 4)
Dressing	Transparent dress	Occlusive devices without gauze not allowed
	Dry gauz:	Occlusion with porous adhesive band imposed (Fig. 5)
Handling	General measure	New caps after any opening of the hubs
	Blood sampling	On antiseptic-impregnated pads
	Drug infusions	Idem, new temporary pipe for each administration
	Cardiac output:	Closed system only, without opening of the circuit
Replacement	72 h intervals	For dress, sets, pipes, and devices
	24 h intervals	For lipid or blood products lines
Removal	In general	Peripheral lines after 72 h Central lines as clinically indicated Prompt removal if vascular accesses not absolutely necessary
	Special conditions	Guidewire exchange systematically performed for any unexplained clinical sepsis ** (see Fig. 6)

Adapted from [9] and [12].

* Precise listing of the material needed, as well as detailed description of the insertion process, must be given to all the staff of the unit including physicians, nurses, and nursing assistants.

** Clinical sepsis was defined as the one of the following clinical signs or symptoms with no other recognized cause: fever (>38°C), hypotension (systolic blood pressure ≤90 mmHg), or oliguria (>20 ml/h), and all of the following: blood culture not performed or no organism/antigen detected in blood, no apparent infection at another site, physician institutes appropriate antimicrobial therapy for sepsis [61].

disinfection) and aseptic techniques for any patient and/or device care is the key requirement of these precautions [43].

However, low-level compliance with hand washing has been repeatedly reported, particularly in ICUs [44,45]. Experience with alcohol-based handrubs has suggested that hand disinfection reduces hand contamination as compared with that achieved with hand washing, and may spare precious time in the ICU, where, in theory, almost two-thirds of work-time of the staff could be required for optimal adherence to infection control guidelines [46,47]. In a French medical ICU, the increase in compliance to hand-hygiene measures — from 42% to 61% — was essentially attributed to the availability of an alcohol solution for handrubs [48]. However, these effects were not sustained, and compliance decreased again over the next few months. A recent hospital-wide campaign promoting an elementary bedside hand-disinfection technique resulted in a sustained improvement in compliance with hand hygiene — from 48% to 66% over a 4-year period [49]. During the same period, the prevalence of overall nosocomial infections decreased significantly, from 17% to 9%.

Technique of catheter insertion

Skin preparation should include the cutting, rather than the shaving, of hair [11,12]. Maximal sterile barrier precautions during insertion — including the use not only of large and fenestrated drapes and sterile gloves, but also of gown, cap, mask, and a large drape — can minimize catheter colonization and subsequent CRIs [50]. Rigorous cleansing and disinfection of the insertion site is regarded as a key point. Solutions of povidone-iodine (10%) and alcohol (70%) are effective, but aqueous chlorhexidine (2%) has been shown to be superior in preventing CVC colonization [51]. An alcohol-based preparation of chlorhexidine gluconate (0.5%) may combine the advantages of a greater antimicrobial spectrum, and a very rapid killing of skin micro-organisms and drying time, at low cost.

Antimicrobial ointments have been used to prevent catheter colonization, but they favor colonization with resistant organisms and are no longer recommended [9].

Site of insertion

Growing evidence has suggested repeatedly that central lines inserted in the jugular site are more likely to be colonized than those inserted by the subclavian route [7,15,18]. This could be related to factors favoring skin colonization, such as proximity of oropharyngeal secretions, higher skin temperature, and difficulties in immobilizing the catheter and maintaining an optimal dressing, particularly in men [7]. Although the reported rate of infection with CVCs inserted through the femoral vein has remained stable since the beginning of the 1990s, and despite potentially less severe complications related to their insertion, they may be associated with a higher rate of deep venous thrombosis, and insufficient data are presently available to recommend their use [52].

The use of tunneled short-term CVCs has been reported to be associated with a decreased rate of CRI, but a recent meta-analysis of randomized controlled trials concluded that it might be the case only for those inserted in the jugular site [53]. An accompanying editorial highlighted the fact that blood-draws through the catheters were not allowed in the study [54], and it was this that determined the positive result of this analysis [55]. The same comment has to be made about the recent large randomized controlled study from the same group [56], in which the authors reported that a catheter-related sepsis occurred in 5 of 168 patients who received a femoral tunneled CVC as compared with 15 of 168 who received a non-tunneled CVC (RR 0.25; 95% CI 0.09–0.72) [56]. The proportion of CVCs used for blood draw is generally not specified in most studies, and many institutions favor arterial lines for this purpose.

Careful fixation of the catheter at the skin exit-site might avoid complications such as leakage of the fixing device and movements through the intradermic portion (Fig. 4).

Figure 4. Promotion of a simple fixation system included in the guidelines (part of the slide-show session included in the educational program) [12]. A: after the insertion of a multiple-lumen central venous catheter in the subclavian position, a wire is passed around the emergence of the catheter and loosely tied. B: the wire is laced around the catheter at its emergence. C: the wire is firmly tied up in order to avoid eventual further slide-up. D: all bloody marks are scrupulously removed, and the exit site is meticulously disinfected before dressing.

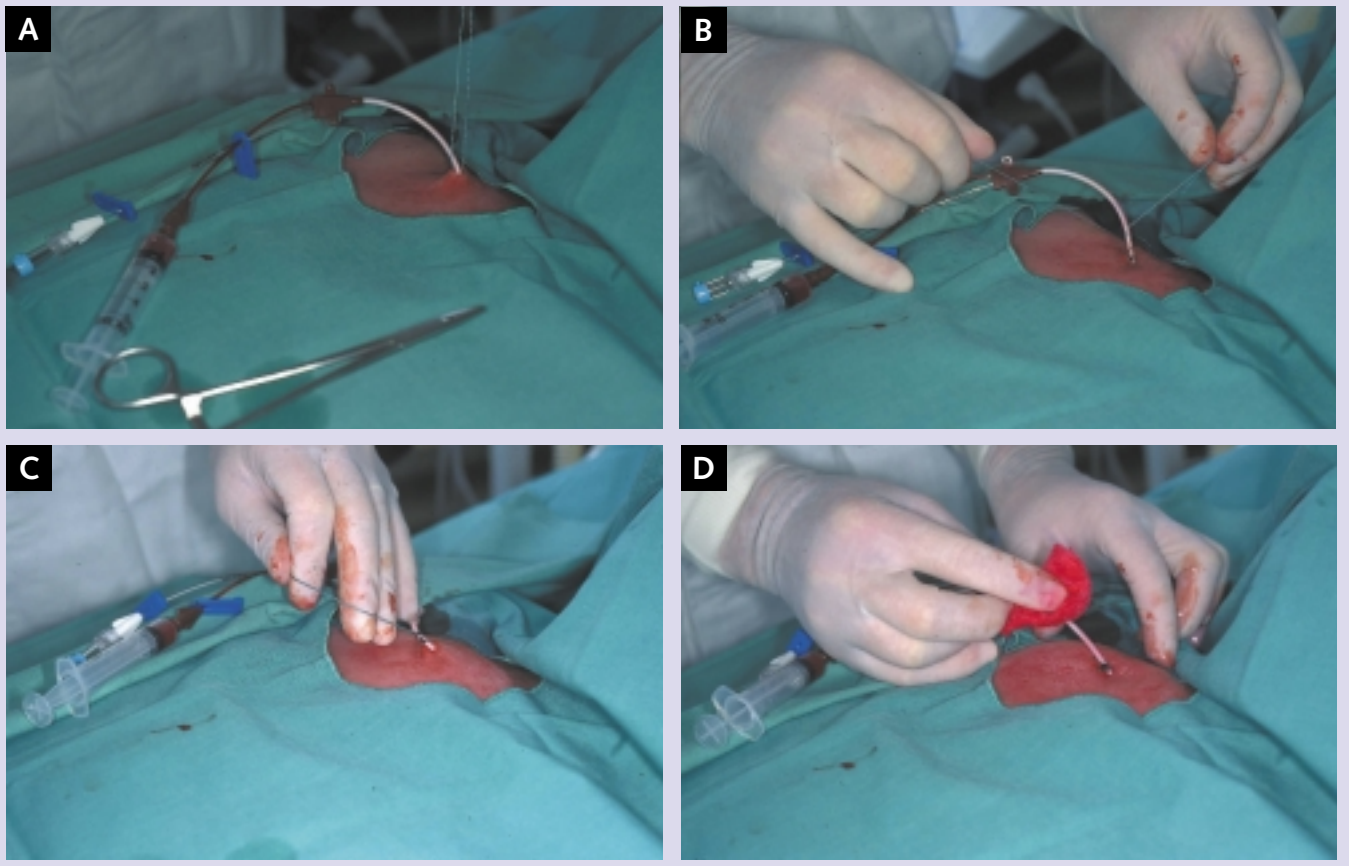


Figure 5. Promotion of a small dry gauze-based dressing included in the guidelines (part of the slide-show session included in the educational program) [12]: The catheter hub is taken away from the neck and dry gauze is disposed over the catheter at its skin exit-site. The dress is ended by apposition of a porous adhesive band, which may easily be taken off after use of an alcohol-based (60–70%) solution of chlorhexidine gluconate 0.5%.

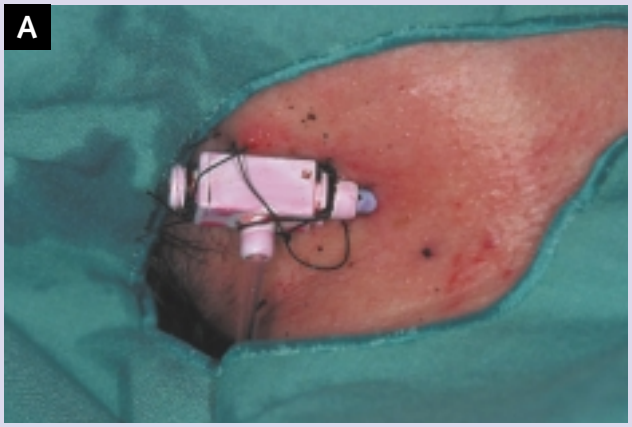
Dressing

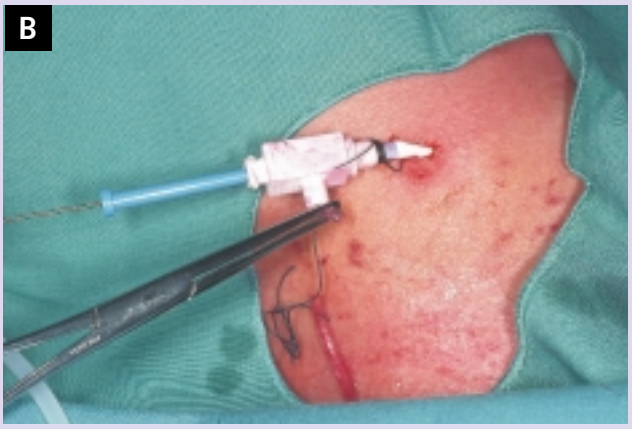
Catheter-site dressing has generated considerable literature for decades, yielding debates and contradictory findings. Semi-permeable transparent dressings are widely used. They are simple to place, allow continuous observation of the skin insertion site, and reduce the risk of extrinsic contamination. However, they promote moisture and bacterial proliferation under the cover and have been associated with higher CRI rates as compared with traditional gauze dressings [57]. Therefore, the use of transparent dressings cannot be recommended in critically ill patients. In addition, a small dressing is easier to secure (Fig. 5). The precise duration a dressing can be safely left on a central line is unknown, but it should be systematically renewed every 48–72 h, if an earlier change is not clinically indicated.

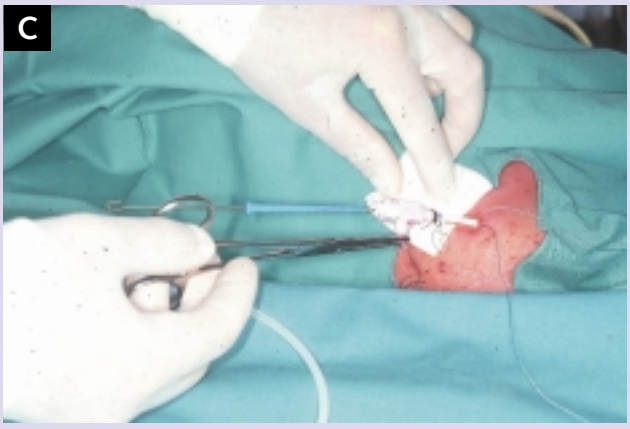
Catheter handling

Recommendations for daily replacement of tubing were made in the 1970s, after several epidemics of BSIs related to intrinsic contamination of intravenous fluid, and have been amply documented [3]. Currently, except for blood products and lipid emulsions, administration sets can be safely replaced every 72 h only [9]. Infusion therapy teams have been reported to decrease CRI rates, but a recent study suggested that appropriately trained personnel might be as effective [58].

Figure 6. Promotion of a guidewire-exchange technique applied to the introducer used in the unit, included in the guidelines (part of the slide-show session included in the educational program) [12]. A: after meticulous disinfection of the skin exit-site, large sterile drapes are installed. B: after introduction of the guidewire by the front port, the lateral line of the introducer is cut over a clip. C: in order to avoid direct contact with a potentially contaminated device, the introducer is removed over the guidewire by traction on the clip over a pad impregnated with a disinfectant solution. The new catheter will be introduced through the guidewire.







A four-fold decrease of CRI rate was reported with the use of an antiseptic hub model as compared to standard model, in a prospective survey of 151 subclavian CVCs inserted for a mean duration of 2 weeks [59]. This was associated with a significant reduction of CR-BSIs attributed to the hub (1% vs. 11%) and with the fact that a smaller proportion of catheters were removed for clinical suspicion of CRI (19% vs. 42%). Such preliminary results call for further randomized trials.

Catheter replacement and/or exchange?

The duration of catheterization has been linked to the risk of CRIs, particularly after 7 days [7,15,60], but systematic routine replacement of central lines has failed to prove its efficacy in decreasing the risk [28]. Catheter exchange over guidewire is discussed in the paragraph on treatment (Fig. 6).

Conclusion

Catheter-related infections should no longer be considered as an indirect tribute to sophisticated care or regarded as a fatality, but must become one of the priority targets of a multidisciplinary approach emphasizing quality-of-care improvement.

References

1. Kohn L, Corrigan J, Donaldson M, editors. *To Err is Human: Building a Safer Health System*. Washington DC: Institute of Medicine, 1999.
2. Bates DW, Miller EB, Cullen DJ et al. Patient risk factors for adverse drug events in hospitalized patients. ADE Prevention Study Group. *Arch Intern Med* 1999;**159**:2553–60.
3. Maki DG, Mermel LA. Infections due to infusion therapy. In: Bennett JV, Brachman PS, editors. *Hospital Infections*. 4th ed. Philadelphia: Lippincott-Raven, 1998:689–724.
4. Monitoring hospital-acquired infections to promote patient safety – United States, 1990–1999. *Morb Mortal Wkly Rep* 2000;**49**:149–53.
5. Maki DG, Stolz SM, Wheeler S et al. Prevention of central venous catheter-related bloodstream infection by use of an antiseptic-impregnated catheter. A randomized, controlled trial. *Ann Intern Med* 1997;**127**:257–66.
6. Raad I, Darouiche RO, Dupuis J et al. Central venous catheter coated with minocycline and rifampine for the prevention of catheter-related colonization and bloodstream infections. A randomized, double-blind trial. *Ann Intern Med* 1997;**127**:267–74.
7. Darouiche RO, Raad II, Heard SO et al. A comparison of two antimicrobial-impregnated central venous catheters. *N Engl J Med* 1999;**340**:1–8.
8. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients. Excess length of stay, extra costs, and attributable mortality. *J Am Med Assoc* 1994;**271**:1598–601.
9. Pearson ML. Guidelines for prevention of intravascular device-related infections. Hospital Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol* 1996;**17**:438–73.
10. Veenstra DL, Saint S, Saha S et al. Efficacy of antiseptic-impregnated central venous catheters in preventing catheter-related bloodstream infection. A meta-analysis. *J Am Med Assoc* 1999;**281**:261–7.
11. Sherertz RJ, Ely EW, Westbrook DM et al. Education of physicians-in-training can decrease the risk for vascular catheter infection. *Ann Intern Med* 2000;**132**:641–8.
12. Eggimann P, Harbarth S, Constantin MN et al. Impact of a prevention strategy targeted at vascular-access care on incidence of infections acquired in intensive care. *Lancet* 2000;**355**:1864–8.
13. incent JL, Bihari DJ, Suter PM et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) study. *J Am Med Assoc* 1995;**274**:639–44.
14. Hampton AA, Sherertz RJ. Vascular-access infections in hospitalized patients. *Surg Clin North Am* 1988;**68**:57–71.
15. Heard SO, Wagle M, Vijayakumar E et al. Influence of triple-lumen central venous catheters coated with chlorhexidine and silver sulfadiazine on the incidence of catheter-related bacteremia. *Arch Intern Med* 1998;**158**:81–7.
16. Pittet D, Wenzel RP. Nosocomial bloodstream infection in the critically ill. *J Am Med Assoc* 1994;**272**:1819–20 (Letter).
17. DiGiovine B, Chenoweth C, Watts C et al. The attributable mortality and costs of primary nosocomial bloodstream infection in the intensive care unit. *Am J Respir Crit Care Med* 1999;**160**:976–81.
18. Rello J, Ochagavia A, Sabanes E et al. Evaluation of outcome of intravenous catheter-related infections in critically ill patients. *Am J Respir Crit Care Med* 2000;**162**:1027–30.
19. Siegman-Igra Y, Anglim AM, Shapiro DE et al. Diagnosis of vascular catheter-related bloodstream infection: A meta-analysis. *J Clin Microbiol* 1997;**35**:928–36.
20. Tennenberg S, Lieser M, McCurdy B et al. A prospective randomized trial of an antibiotic- and antiseptic-coated central venous catheter in the prevention of catheter-related infections. *Arch Surg* 1997 ;**132**:1348–51.
21. Raad II, Sabbagh MF. Optimal duration of therapy for catheter-related Staphylococcus aureus bacteremia: A study of 55 cases and review. *Clin Infect Dis* 1992;**14**:75–82.
22. Maki DG, Weise CE, Sarafin HW. A semiquantitative culture method for identifying intravenous-catheter-related infection. *N Engl J Med* 1977;**296**:1305–9.
23. Raad I, Costerton W, Sabharwal U et al. Ultrastructural analysis of indwelling vascular catheters: A quantitative relationship between luminal colonization and duration of placement. *J Infect Dis* 1993;**168**:400–7.

24. Lew DP, Pittet D, Waldvogel FA. Infections that complicate the insertion of prosthetic devices. In: Mayhall G, editor. *Hospital Epidemiology and Infection Control*. Williams & Willkins, Baltimore, Philadelphia, Hong Kong, London, Munich, Sydney, Toronto1996:731–48.
25. Pittet D, Hulliger S, Auckenthaler R. Intravascular device-related infections in critically ill patients. *J Chemother* 1995;**7**:55–66.
26. Salzman MB, Isenberg HD, Shapiro JF et al. A prospective study of the catheter hub as the portal of entry for microorganisms causing catheter-related sepsis in neonates. *J Infect Dis* 1993;**167**:487–90.
27. Anaissie EJ, Rex JH, Uzun O et al. Predictors of adverse outcome in cancer patients with candidemia. *Am J Med* 1998;**104**:238–45.
28. Cobb DK, High KP, Sawyer RG et al. A controlled trial of scheduled replacement of central venous and pulmonary-artery catheters. *N Engl J Med* 1992;**327**:1062–8.
29. Badley AD, Steckelberg JM, Wollan PC et al. Infectious rates of central venous pressure catheters: Comparison between newly placed catheters and those that have been changed. *Mayo Clin Proc* 1996;**71**:838–46.
30. Marr KA, Sexton DJ, Conlon PJ et al. Catheter-related bacteremia and outcome of attempted catheter salvage in patients undergoing hemodialysis. *Ann Intern Med* 1997;**127**:275–80.
31. Rosen AB, Fowler VG Jr, Corey GR et al. Cost-effectiveness of transesophageal echocardiography to determine the duration of therapy for intravascular catheter-associated Staphylococcus aureus bacteremia. *Ann Intern Med* 1999;**130**:810–20.
32. Rangel-Frausto MS, Wiblin T, Blumberg HM et al. National epidemiology of mycoses survey (NEMIS): Variations in rates of bloodstream infections due to Candida species in seven surgical intensive care units and six neonatal intensive care units. *Clin Infect Dis* 1999;**29**:253–8.
33. Raad I. Intravascular-catheter-related infections. *Lancet* 1998;**351**:893–8.
34. Mermel LA. Prevention of intravascular catheter-related infections. *Ann Intern Med* 2000;**132**:391–402.
35. Rackoff WR, Weiman M, Jakobowski D et al. A randomized, controlled trial of the efficacy of a heparin and vancomycin solution in preventing central venous catheter infections in children. *J Pediatr* 1995;**127**:147–51.
36. Veenstra DL, Saint S, Sullivan SD. Cost-effectiveness of antiseptic-impregnated central venous catheter for the prevention of catheter-related bloodstream infection. *J Am Med Assoc* 1999;**282**:554–60.
37. Logghe C, Van Ossel C, D'Hoore W et al. Evaluation of chlorhexidine and silver-sulfadiazine impregnated central venous catheters for the prevention of bloodstream infection in leukaemic patients: A randomized controlled trial. *J Hosp Infect* 1997;**37**:145–56.
38. Marik PE, Abraham G, Careau P et al. The ex vivo antimicrobial activity and colonization of two antimicrobial-bonded central venous catheters. *Crit Care Med* 1999;**27**:1128–31.
39. Walder B, Pittet D, Tramer M. Benefit of antiseptic and antimicrobial coating of central venous catheters: A systematic review. *Schweiz Med Wochenschr* 1999;**129**:22S.
40. Kretzer EK, Larson EL. Behavioral interventions to improve infection control practices. *Am J Infect Control* 1998;**26**:245–53.
41. Greco PJ, Eisenberg JM. Changing physicians' practices. *N Engl J Med* 1993;**329**:1271–3.
42. Garner JS. Guidelines for isolation precautions in hospitals. The Hospital Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol* 1996;**17**:53–80.
43. Larson EL. APIC guidelines for handwashing and hand antisepsis in health care settings. *Am J Infect Control* 1995;**23**:251–69.
44. Sproat LJ, Inglis TJ. A multicentre survey of hand hygiene practice in intensive care units. *J Hosp Infect* 1994;**26**:137–48.
45. Pittet D, Mourouga P, Perneger TV, and the members of the infection control program. Compliance with handwashing in a teaching hospital. *Ann Intern Med* 1999;**130**:126–30.
46. Ehrenkranz NJ, Alfonso BC. Failure of bland soap handwash to prevent hand transfer of patient bacteria to urethral catheters. *Infect Control Hosp Epidemiol* 1991;**12**:654–62.
47. Pittet D, Dharan S, Touveneau S et al. Bacterial contamination of the hands of hospital staff during routine patient care. *Arch Intern Med* 1999;**159**:821–6.
48. Maury E, Alzieu M, Baudel JL et al. Availability of an alcohol solution can improve hand disinfection compliance in an intensive care unit. *Am J Respir Crit Care Med* 2000;**162**:324–7.
49. Pittet D, Hugonnet S, Harbarth S et al. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. *Lancet* 2000 (in press)
50. Raad II, Hohn DC, Gilbreath BJ et al. Prevention of central venous catheter-related infections by using maximal sterile barrier precautions during insertion. *Infect Control Hosp Epidemiol* 1994;**15**:231–8.
51. Maki DG, Ringer M, Alvarado CJ. Prospective randomised trial of povidone-iodine, alcohol, and chlorhexidine for prevention of infection associated with central venous and arterial catheters. *Lancet* 1991;**338**:339–43.
52. Smyrnios NA, Irwin RS. The jury on femoral vein catheterization is still out. *Crit Care Med* 1997;**25**:1943–6.
53. Randolph AG, Cook DJ, Gonzales CA, Brun-Buisson C. Tunneling short-term central venous catheters to prevent catheter-related infections: A meta-analysis of randomized, controlled trials. *Crit Care Med* 1998;**26**:1452–7.
54. Timsit JF, Sebille V, Farkas JC et al. Effect of subcutaneous tunneling on internal jugular catheter-related sepsis in critically ill patients: A prospective randomized multicenter study. *J Am Med Assoc* 1996;**276**:1416–20.
55. Mermel LA. Central venous catheter-related infections and their prevention: Is there enough evidence to recommend tunneling for short-term use ? *Crit Care Med* 1998;**26**:1315–6.

56. Timsit JF, Bruneel F, Cheval C et al. Use of tunneled femoral catheters to prevent catheter-related infections. *Ann Intern Med* 1999;**130**:729–35.
57. Hoffmann KK, Weber DJ, Samsa GP et al. Transparent polyurethane film as an intravenous catheter dressing. A meta-analysis of the infection risks. *J Am Med Assoc* 1992;**267**:2072–6.
58. Abi-Said D, Raad I, Umphrey J et al. Infusion therapy team and dressing changes of central venous catheters. *Infect Control Hosp Epidemiol* 1999;**20**:101–5.
59. Segura M, Alvarez-Lerma F, Tellado JM et al. A clinical trial on the prevention of catheter-related sepsis using a new hub model. *Ann Surg* 1996;**223**:363–9.
60. Souweine B, Traore O, Aublet-Cuvelier B et al. Dialysis and central venous catheter infections in critically ill patients: Results of a prospective study. *Crit Care Med* 1999;**27**:2394–8.
61. Garner JS, Jarvis WR, Emori TG et al. CDC definitions for nosocomial infections. *Am J Infect Control* 1988;**16**:128–40.
62. Bach A, Schmidt H, Bottiger B et al. Retention of antibacterial activity and bacterial colonization of antiseptic-bonded central venous catheters. *J Antimicrob Chemother* 1996;**37**:315–22.
63. Hannan M, Juste RN, Umasanker S et al. Antiseptic-bonded central venous catheters and bacterial colonisation. *Anaesthesia* 1999;**54**:868–72.
64. Loo S, van Heerden PV, Gollege CL et al. Infection in central lines: Antiseptic-impregnated vs standard non-impregnated catheters. *Anaesth Intensive Care* 1997;**25**:637–9.
65. Marik PE, Abraham G, Careau P et al. The ex vivo antimicrobial activity and colonization rate of two antimicrobial-bonded central venous catheters. *Crit Care Med* 1999;**27**:1128–31.
66. van Heerden PV, Webb SA, Fong S et al. Infection in central lines: antiseptic-impregnated vs standard non-impregnated catheters. *Anaesth Intensive Care* 1997;**25**:637–9.
67. Legras A, Malvy D, Quinioux AI et al. Nosocomial infections: Prospective survey of incidence in five French intensive care units. *Intensive Care Med* 1998;**24**:1040–6.
68. Singh-Naz N, Sprague BM, Patel KM et al. Risk assessment and standardized nosocomial infection rate in critically ill children. *Crit Care Med* 2000;**28**:2069–75.
69. Gastmeier P, Hentschel J, de Veer I et al. Device-associated nosocomial infection surveillance in neonatal intensive care using specified criteria for neonates. *J Hosp Infect* 1998;**38**:51–60.
70. Finkelstein R, Rabino G, Kassis I et al. Device-associated, device-day infection rates in an Israeli adult general intensive care unit. *J Hosp Infect* 2000;**44**:200–5.
71. Simon A, Bindl L, Kramer MH. Surveillance of nosocomial infections: Prospective study in a pediatric intensive care unit. Background, patients and methods. *Klin Padiatr* 2000;**212**:2–9.
72. Weber JM, Sheridan RL, Pasternack MS et al. Nosocomial infections in pediatric patients with burns. *Am J Infect Control* 1997;**25**:195–201.
73. Dettenkofer M, Ebner W, Hans FJ et al. Nosocomial infections in a neurosurgery intensive care unit. *Acta Neurochir (Wien)* 1999;**141**:1303–8.
74. Rose R, Hunting KJ, Townsend TR et al. Morbidity/mortality and economics of hospital-acquired blood stream infections: A controlled study. *South Med J* 1977;**70**:1267–9.
75. Spengler RF, Greenough WB III. Hospital costs and mortality attributed to nosocomial bacteremias. *J Am Med Assoc* 1978;**240**:2455–8.
76. Wey SB, Motomi M, Pfaller MA et al. Hospital-acquired candidemia. The attributable mortality and excess length of stay. *Arch Intern Med* 1988;**148**:2642–5.
77. Martin MA, Pfaller MA, Wenzel RP. Coagulase-negative staphylococcal bacteremia. Mortality and hospital stay. *Ann Intern Med* 1989;**110**:9–16.
78. Forgacs IC, Eykyn SJ, Bradley RD. Serious infection in the intensive therapy unit: A 15-year study of bacteraemia. *Q J Med* 1986;**60**:773–9.
79. Smith RL, Meixler SM, Simberkoff MS. Excess mortality in critically ill patients with nosocomial bloodstream infections. *Chest* 1991;**100**:164–7.
80. Rello J, Ricart M, Mirelis B et al. Nosocomial bacteremia in a medical-surgical intensive care unit: Epidemiologic characteristics and factors influencing mortality in 111 episodes [see comments]. *Intensive Care Med* 1994;**20**:94–8.
81. Soufir L, Timsit JF, Mahe C et al. Attributable morbidity and mortality of catheter-related septicemia in critically ill patients: A matched, risk-adjusted, cohort study. *Infect Control Hosp Epidemiol* 1999;**20**:396–401.
82. Kite P, Dobbins BM, Wilcox MH et al. Rapid diagnosis of central-venous-catheter-related bloodstream infection without catheter removal. *Lancet* 1999;**354**:1504–7.
83. Brun-Buisson C, Abrouk F, Legrand P et al. Diagnosis of central venous catheter-related sepsis. *Arch Intern Med* 1987;**147**:873–7.
84. Sherertz RJ, Raad II, Belani A et al. Three-year experience with sonicated vascular catheter cultures in a clinical microbiology laboratory. *J Clin Microbiol* 1990;**28**:76–82.
85. Blot F, Nitenberg G, Chachaty E et al. Diagnosis of catheter-related bacteremia: A prospective comparison of the time to positivity of hub-blood versus peripheral-blood cultures. *Lancet* 1999;**354**:1071–7.
86. Rushforth JA, Hoy CM, Kite P et al. Rapid diagnosis of central venous catheter sepsis. *Lancet* 1993;**342**:402–3.